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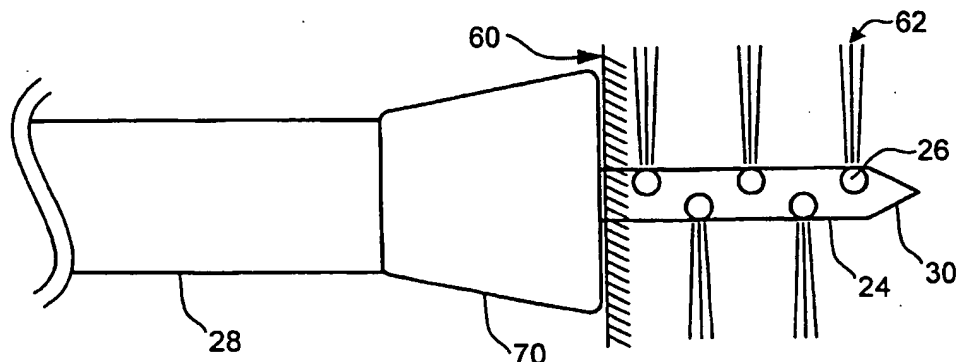
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(54) Title: LATERAL NEEDLE-LESS INJECTION APPARATUS AND METHOD



(57) Abstract: A device and method for delivering and injecting fluid into heart tissue utilizing laterally directed injection ports to increase injectate (fluid) retention in the heart tissue. The catheter includes a shaft having an infusion lumen extending therethrough, wherein the distal end of the shaft includes a penetrating member having one or more injection ports. The penetrating member penetrates the heart tissue in a first direction, and the injection port or ports direct fluid in a second direction different from the first direction. By injecting the fluid or fluid in a direction different than the penetration direction, fluid leakage from the injection site is reduced and a greater volume of tissue is treated for a single primary injection.

WO 01/41657 A1

## LATERAL NEEDLE-LESS INJECTION APPARATUS AND METHOD

### Related Applications

This application is related to co-pending U.S. Patent Application Serial Number 09/457,453, filed on December 8, 1999, entitled INJECTION ARRAY  
5 APPARATUS AND METHOD; co-pending U.S. Patent Application Serial Number 09/457,254, filed on December 8, 1999, entitled LATERAL NEEDLE INJECTION APPARATUS AND METHOD; and co-pending U.S. Patent Application Serial Number 09/456,456, filed on December 8, 1999, entitled NEEDLE-LESS INJECTION APPARATUS AND METHOD.

### Field of the Invention

10 The present invention generally relates to delivering and injecting fluid into heart tissue. More specifically, the present invention relates to delivering and injecting fluid into heart tissue utilizing laterally directed injection ports.

### Background of the Invention

15 Injection catheters may be used to inject therapeutic or diagnostic agents into a variety of organs, such as the heart. In the case of injecting a therapeutic agent into the heart, 27 or 28 gauge needles are generally used to inject solutions carrying genes, proteins, or drugs directly into the myocardium. A typical volume of an agent delivered to an injection site is about 100 microliters. A limitation to this method of  
20 delivering therapeutic agents to the heart is that the injected fluid tends to leak from the site of the injection after the needle is disengaged from the heart. In fact, fluid may continue to leak over several seconds. In the case of dynamic organs such as the heart, there may be more pronounced leakage with each muscle contraction.

Therapeutic and diagnostic agents may be delivered to a portion of the heart as  
25 part of a percutaneous myocardial revascularization (PMR) procedure. PMR is a procedure which is aimed at assuring that the heart is properly oxygenated. Assuring that the heart muscle is adequately supplied with oxygen is critical to sustaining the life of a patient. To receive an adequate supply of oxygen, the heart muscle must be well perfused with blood. In a healthy heart, blood perfusion is accomplished with a  
30 system of blood vessels and capillaries. However, it is common for the blood vessels to become occluded (blocked) or stenotic (narrowed). A stenosis may be formed by an atheroma which is typically a harder, calcified substance which forms on the walls of a blood vessel.

Historically, individual stenotic lesions have been treated with a number of medical procedures including coronary bypass surgery, angioplasty, and atherectomy. Coronary bypass surgery typically involves utilizing vascular tissue from another part of the patient's body to construct a shunt around the obstructed vessel. Angioplasty techniques such as percutaneous transluminal angioplasty (PTA) and percutaneous transluminal coronary angioplasty (PTCA) are relatively non-invasive methods of treating a stenotic lesion. These angioplasty techniques typically involve the use of a guide wire and a balloon catheter. In these procedures, a balloon catheter is advanced over a guide wire such that the balloon is positioned proximate a restriction in a diseased vessel. The balloon is then inflated and the restriction in the vessel is opened. A third technique which may be used to treat a stenotic lesion is atherectomy. During an atherectomy procedure, the stenotic lesion is mechanically cut or abraded away from the blood vessel wall.

Coronary by-pass, angioplasty, and atherectomy procedures have all been found effective in treating individual stenotic lesions in relatively large blood vessels. However, the heart muscle is perfused with blood through a network of small vessels and capillaries. In some cases, a large number of stenotic lesions may occur in a large number of locations throughout this network of small blood vessels and capillaries. The torturous path and small diameter of these blood vessels limit access to the stenotic lesions. The sheer number and small size of these stenotic lesions make techniques such as cardiovascular by-pass surgery, angioplasty, and atherectomy impractical.

When techniques which treat individual lesion are not practical, percutaneous myocardial revascularization (PMR) may be used to improve the oxygenation of the myocardial tissue. A PMR procedure generally involves the creation of holes, craters or channels directly into the myocardium of the heart. In a typical PMR procedure, these holes are created using radio frequency energy delivered by a catheter having one or more electrodes near its distal end. After the wound has been created, therapeutic agents are sometimes ejected into the heart chamber from the distal end of a catheter.

Positive clinical results have been demonstrated in human patients receiving PMR treatments. These results are believed to be caused in part by blood flowing within the heart chamber through channels in myocardial tissue formed by PMR. Increased blood flow to the myocardium is also believed to be caused in part by the

healing response to wound formation. Specifically, the formation of new blood vessels is believed to occur in response to the newly created wound. This response is sometimes referred to as angiogenesis. After the wound has been created, therapeutic agents which are intended to promote angiogenesis are sometimes injected into the heart chamber. A limitation of this procedure is that the therapeutic agent may be quickly carried away by the flow of blood through the heart.

In addition to promoting increased blood flow, it is also believed that PMR improves a patient's condition through denervation. Denervation is the elimination of nerves. The creation of wounds during a PMR procedure results in the elimination of nerve endings which were previously sending pain signals to the brain as a result of hibernating tissue.

Currently available injection catheters are not particularly suitable for accurately delivering small volumes of therapeutic agents to heart tissue. Improved devices and methods are desired to address the problems associated with retention of the agent in the heart tissue as discussed above. This is particularly true for agents carrying genes, proteins, or other angiogenic drugs which may be very expensive, even in small doses.

#### Summary of the Invention

The present invention provides an improved apparatus and method for delivering and injecting fluid into heart tissue. The present invention addresses the problems associated with retention of the fluid in the heart tissue by utilizing one or more laterally directed injection ports. The present invention may be used to deliver genes, proteins, or drugs directly into the myocardium for purposes of myocardial revascularization.

In an exemplary embodiment, the present invention provides a catheter having a shaft with an infusion lumen extending therethrough. The distal end of the shaft includes a penetrating member having one or more injection ports. The penetrating member penetrates the heart tissue in a first direction, and the injection port or ports direct fluid in a second direction different from the first direction. By injecting the fluid or fluids in a direction different than the penetration direction, fluid leakage from the injection site is reduced and a greater volume of tissue is treated for a single primary injection.

The injection ports may have a diameter of approximately 1 to 500 microns, depending on the desired injection parameters. The second direction may be at an

angle of about 5 to about 90 degrees relative to the first direction, and the first direction is preferably orthogonal to the heart tissue at the injection site.

The catheter may include a sheath disposed about the shaft. The distal end of the sheath may include a suction head for stabilizing the distal end of the catheter upon the application of suction to the sheath.

The present invention also provides a method of delivering a fluid to heart tissue including the steps of: navigating a catheter substantially as described above in a patient's body until the distal end of the catheter is positioned adjacent the injection site; actuating the penetrating member such that the penetrating member penetrates the heart tissue in a first direction; and injecting the fluid into the heart tissue via the injection ports at a second direction different than the first direction. This method reduces fluid leakage from the injection site and treats a greater volume of tissue for a single primary injection.

#### Brief Description of the Drawings

Fig. 1A is a plan view of a catheter system in accordance with an exemplary embodiment of the present invention;

Fig. 1B is an enlarged detailed view of the distal end of the catheter illustrated in Fig. 1A;

Fig. 2 is a further enlarged view of the distal end of the catheter illustrated in Fig. 1A;

Fig. 3 is a lateral cross-sectional view taken along line 3-3 in Fig. 2;

Fig. 4 is a lateral cross-sectional view taken along line 4-4 in Fig. 2;

Fig. 5 is a simplified longitudinal cross-sectional view of the penetrating member;

Figs. 6A-6C illustrate a sequence of steps for using the system illustrated in Fig 1A; and

Figs. 7A-7C illustrate a sequence of steps for using an alternative embodiment of the system illustrated in Fig 1A, incorporating a stabilizing suction head.

#### Detailed Description of the Invention

The following detailed description should be read with reference to the drawings in which similar elements in different drawings are numbered the same. The drawings, which are not necessarily to scale, depict illustrative embodiments and are not intended to limit the scope of the invention.

Refer now to Figure 1A which illustrates a plan view of a catheter system 10 in accordance with an exemplary embodiment of the present invention. Catheter system 10 includes a catheter 12 having an elongate shaft 14. A manifold 16 is connected to the proximal end of the elongate shaft 14. The elongate shaft 14 includes a distal portion 18 which is illustrated in greater detail in Figure 1B.

A pressurized fluid source 20 is connected to the catheter 12 by way of the manifold 16. Optionally, a vacuum source may be coupled to the side arm of the manifold 16. The pressurized fluid source 20 may comprise a conventional syringe or an automated pressure source such as a high pressure injection system. An example of a high pressure injection system is disclosed in U.S. Patent No. 5,520,639 to Peterson et al. which is hereby incorporated by reference. The system may be gas driven, such as with carbon dioxide, or it may be mechanically driven, with a spring, for example, to propel the solution. Similarly, vacuum source 22 may comprise a conventional syringe or other suitable vacuum means such as a vacuum bottle.

Refer now to Figure 1B which illustrates an enlarged detailed view of the distal portion 18 of the elongate shaft 14. The distal portion 18 of the elongate shaft 14 includes a penetrating member 24 coaxially disposed in an elongate outer sheath 28. The penetrating member 24 contains a plurality of injection ports 26 disposed adjacent the distal end thereof. The injection ports 26 are in fluid communication with the pressurized fluid source 20 via penetrating member 24 and manifold 16.

With reference to Figure 2, the penetrating member 24 includes a sharpened distal end 30 to facilitate easy penetration of tissue. The injection ports 26 extend through the wall of the penetrating member 24. The injection ports 26 each have an axis that is at an angle with the longitudinal axis of the penetrating member 24. The axis of each injection port 26 may be orthogonal to the axis of the penetrating member 24 or any other desired angle. The angle of the axis of each injection port 26 determines in part the penetration angle of the fluid as discussed in greater detail with reference to Figures 6A - 6C.

With reference to Figure 3, a lateral cross-sectional view taken along line 3-3 in Figure 2 is shown. The shaft 14 includes an annular lumen 36 defined between the interior of the sheath 28 and the exterior of the penetrating member 24. The annular lumen 36 may be used to infuse fluids for purposes of fluoroscopic visualization and/or aspiration. Alternatively, the annular lumen 36 may be used to facilitate the

application of suction for stabilization purposes as will be discussed in greater detail with reference to Figures 7A-7C.

The elongate shaft 14 has characteristics (length, profile, flexibility, pushability, trackability, etc.) suitable for navigation from a remote access site to the treatment site within the human body. For example, the elongate shaft 14 may have characteristics suitable for intravascular navigation to the coronary tissue from a remote access site in the femoral artery. Alternatively, the elongate shaft 14 may have characteristics suitable for transthoracic navigation to the coronary tissue from a remote access point in the upper thorax. Those skilled in the art will recognize that the shaft 14 may have a wide variety of dimensions, materials, constructions, etc. depending on the particular anatomy being traversed.

— Refer now to Figure 4 which illustrates a lateral cross-sectional view taken along line 4-4 in Figure 2. Penetrating member 24 includes an internal lumen 38 in fluid communication with the injection ports 26. The injection ports 26 are in fluid communication with the pressurized fluid source 20 via lumen 38 of penetrating member 24 such that fluid may be readily delivered from the pressurized fluid source 20 through the shaft 14 and into the heart tissue being treated. Fluid communication between the pressurized fluid source 20 and the injection ports 26 may be defined by a direct connection between the proximal end of the penetrating member 24 and the source 20 via manifold 16. Such fluid communication may also be defined in part by an intermediate tube connected to the proximal end of the penetrating member 24.

The penetrating member 24 may have a length slightly greater than the length of the outer sheath 28, with a penetrating length of approximately 1 to 10 mm. The inside diameter of the penetrating member 24 should be sufficiently large to accommodate the desired flow rate of fluid, but sufficiently small to reduce the amount of fluid waste remaining in the lumen 38 after the procedure is complete. For example, the penetrating member 24 may have an inside diameter in the range of 1 to 250 microns and an outside diameter in the range of 10 microns to 1.25 mm. The penetrating member 24 may be formed of stainless steel or other suitable material such as nickel titanium alloy. The injection ports 26 may have a diameter ranging from approximately 1 to 500 microns.

Refer now to Figures 6A-6C which illustrate operation of the catheter system 10. The heart tissue 60 (i.e., myocardium) may be accessed from the interior of the heart by, for example, navigating the catheter 12 through the vascular system into a

chamber of the heart. Alternatively, the heart tissue 60 may be accessed from the exterior of the heart by, for example, transthoracic minimally invasive surgery in which the catheter 12 is navigated through the upper thoracic cavity adjacent the epicardium of the heart.

5        Regardless of the approach, the distal portion 18 of the catheter 12 is positioned adjacent the desired treatment site of the heart tissue 60 utilizing conventional visualization techniques such as x-ray, fluoroscopy or endoscopic visualization. While positioning the catheter 12, the penetrating member 24 may be partially retracted in the outer sheath 28 such that only the distal end 30 of the  
10       penetrating member 24 is exposed, or fully retracted such that the entire penetrating member 24 is contained within the outer sheath 28.

      With the distal portion 18 positioned adjacent the heart tissue 60 as shown in Figure 6A, the penetrating member 24 is advanced into the heart tissue 60 until the distal end 30 of the penetrating member 24 reaches a sufficient depth to position the  
15       injection ports 26 completely within the tissue 60 as shown in Figure 6B. This position may be confirmed by injecting radiopaque contrast media or colored dye through the inner lumen 38 of the penetrating member 24 such that the contrast media or dye exits the injection ports 26.

      Once in position, fluid 62 may be infused from the pressurized fluid source 20  
20       through the lumen 38 of the penetrating member and through the injection ports 26 and into the heart tissue 60. After the fluid 62 has been delivered via the injection lumens in the injection ports 26, the penetrating member 24 may be retracted into the outer sheath 28. After retraction, the entire catheter 12 may be removed from the patient.

25       The pressure applied by the pressurized fluid source 20 to deliver the fluid 62 into the heart tissue 60 may vary depending on the desired result. For example, a relatively low pressure of approximately .01 to 1 ATM may be utilized to deliver the fluid 62 into the heart tissue 60 thereby minimizing trauma to the tissue adjacent the injection site. Alternatively, a relatively high pressure of approximately 10 to 300  
30       ATM may be utilized to increase the depth penetration of the fluid 62 into the heart tissue 60 and/or to dispense the solution throughout the injected tissue.

      The penetration depth of the fluid 62 into the tissue 60 influences fluid retention, the volume of tissue 60 treated and the degree of trauma to the tissue 60. The penetration depth of the fluid 62 is dictated, in part, by the exit velocity of the



fluid 62, the size of the fluid stream 62, and the properties of the tissue 60. The exit velocity, in turn, depends on the applied pressure of the pressurized fluid source 20, the drag or pressure drop along the length of the lumen 38 and the ports 26, and the cross-sectional area or size of the ports 26. The size of the fluid stream 62 also depends on the size of the ports 26. Thus, assuming the treatment site dictates the tissue 60 properties, the penetration depth may be selected by adjusting the applied pressure of the pressurized fluid source 20, the size and length of the lumen 38, and the cross-sectional area of the ports 26. By adjusting these parameters, fluid retention, treated tissue volume and degree of trauma may be modified as required for the particular clinical application.

As can be appreciated from the illustration of Figure 6C, by injecting the fluid 62 in a direction different from the direction of penetration of the penetrating member 24, the fluid 62 will be retained within the heart tissue 60. Retention of the fluid 62 in the heart tissue 60 is primarily accomplished by forming the injection ports at an angle relative to the direction of penetration of the penetrating member 24, i.e., the longitudinal axis of the penetrating member 24. In addition to providing better retention of the fluid 62 within the heart tissue 60, this arrangement also allows for a greater volume of heart tissue 60 to be treated with a single primary penetration.

In an embodiment of the present invention, a low volume (several microliters but less than 100 microliters by a single injection) of solution is delivered to the heart such that it may absorb the delivered solution within the time frame of the injection. In contrast to higher volume injections, the heart is more capable of absorbing these low volumes. The effect of the low volume injection is to minimize expulsion by the tissue. In order to deliver the entire dose of virus, it may be desirable or necessary to concentrate the injection (i.e., deliver the same number of viral particles or micrograms of protein, typically delivered in 100 $\mu$ l, in a volume of 10 $\mu$ l) or keep the concentration of virus the same as that typically used, but increase the number of injections from 10 (typical) to 20, 30, or more.

Each injectate may also be delivered in a prolonged manner such that the heart can absorb the solution as it is being injected (rate of delivery  $\leq$  rate of tissue absorption). For instance, the injection can be delivered at a defined flow rate using a syringe pump. The time of injection will depend on the volume to be delivered. For example, low volumes (a few microliters) may be delivered in under a minute while higher volumes (10 to 100 $\mu$ l or more) may be delivered over several minutes. In this

instance, it may be beneficial to include a method which gently attaches the injection catheter to the wall of the heart, for instance suction or vacuum.

Thus, to accomplish this result, the injection ports 26 may be formed at an angle to the longitudinal axis of the penetrating member 24. Preferably, the axes of the injection ports 26 are generally lateral to the longitudinal axis of the penetrating member 24. However, the axes of the injection ports 26 may be formed at an angle of about 5 to about 90 degrees relative to the axis of the penetrating member 24 to accomplish essentially the same result. Also preferably, the penetrating member 24 penetrates the heart tissue 60 in a direction generally orthogonal to the surface of the heart tissue 60 adjacent the injection site.

Refer now to Figures 7A-7C which illustrate operation of an alternative embodiment of the catheter system 10. In this particular embodiment, the distal portion of the catheter 12 incorporates a suction head 70 connected to the distal head of the outer sheath 28. The suction head 70 comprises a flexible tubular member having a generally conical shape. The suction head 70 has an interior which is in fluid communication with the inner lumen 36 of the outer sheath 28. As mentioned previously, the inner lumen 36 of the outer sheath 28 is in fluid communication with the vacuum source 22. By actuating the vacuum source 22, suction is applied to the suction head via the inner lumen 36 of the outer sheath 28.

The suction head is positioned adjacent the heart tissue 60 as illustrated in Figure 7A. The suction head 70 grasps the surface of the heart tissue 60 thereby stabilizing the distal portion 18 of the catheter 12. This is particularly beneficial when treating tissue in a dynamic setting such as when the heart is beating. Absent a stabilizing means such as suction head 70, it may be difficult to maintain the distal portion 18 in a relatively fixed position if the treatment site is not stationary. Those skilled in the art will recognize that other stabilizing means may be utilized such as removable screw anchors, miniature forceps, etc.

After suction is applied to the suction head 70 thereby stabilizing the distal portion 18 of the catheter 12, the penetrating member 24 is advanced into the heart tissue 60 as illustrated in Figure 7B. Once the injection ports 26 of the penetrating member 24 are completely embedded within the heart tissue 60, fluid 62 may be delivered into the heart tissue 60 via the injection ports 26 as discussed previously.

After the fluid 62 has been delivered to the heart tissue 60, the penetrating member 24 may be retracted into the outer sheath 28. After retracting the penetrating

member 24, the suction applied by the suction head 70 is terminated to release the distal portion 18 of the catheter from the heart tissue 60. The entire catheter system 12 may then be removed from the patient.

From the foregoing, it is apparent that the present invention provides a device  
5 and method for delivering and injecting fluid into heart tissue to improve delivery efficiency. This is accomplished by utilizing injection ports which direct fluid in a direction different from the direction of penetration of the penetrating member. Thus, fluid leakage from the injection site is reduced and the fluid is distributed over a greater volume of tissue.

10 Although treatment of the heart is used as an example herein, the medical devices of the present invention are useful for treating any mammalian tissue or organ. Non-limiting examples include tumors; organs including but not limited to the heart, lung, brain, liver, kidney, bladder, urethra and ureters, eye, intestines, stomach, pancreas, ovary, prostate; skeletal muscle; smooth muscle; breast, cartilage and bone.

15 The terms "therapeutic agents" and "drugs" are used interchangeably herein and include pharmaceutically active compounds, cells, nucleic acids with and without carrier vectors such as lipids, compacting agents (such as histones), virus, polymers, proteins, and the like, with or without targeting sequences.

Specific examples of therapeutic agents used in conjunction with the present  
20 invention include, for example, proteins, oligonucleotides, ribozymes, anti-sense genes, DNA compacting agents, gene/vector systems (*i.e.*, anything that allows for the uptake and expression of nucleic acids), nucleic acids (including, for example, recombinant nucleic acids; naked DNA, cDNA, RNA; genomic DNA, cDNA or RNA in a non-infectious vector or in a viral vector which may have attached peptide  
25 targeting sequences; antisense nucleic acid (RNA or DNA); and DNA chimeras which include gene sequences and encoding for ferry proteins such as membrane translocating sequences ("MTS") and herpes simplex virus-1 ("VP22")), and viral, liposomes and cationic polymers that are selected from a number of types depending on the desired application. Other pharmaceutically active materials include anti-  
30 thrombogenic agents such as heparin, heparin derivatives, urokinase, and PPACK (dextrophenylalanine proline arginine chloromethylketone); antioxidants such as probucol and retinoic acid; angiogenic and anti-angiogenic agents; agents blocking smooth muscle cell proliferation such as rapamycin, angiopeptin, and monoclonal antibodies capable of blocking smooth muscle cell proliferation; anti-inflammatory

agents such as dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, acetyl salicylic acid, and mesalamine; calcium entry blockers such as verapamil, diltiazem and nifedipine; antineoplastic / antiproliferative / anti-mitotic agents such as paclitaxel, 5-fluorouracil, methotrexate, doxorubicin, daunorubicin, cyclosporine, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin and thymidine kinase inhibitors; antimicrobials such as triclosan, cephalosporins, aminoglycosides, and nitrofurantoin; anesthetic agents such as lidocaine, bupivacaine, and ropivacaine; nitric oxide (NO) donors such as lisidomine, molsidomine, L-arginine, NO-protein adducts, NO-carbohydrate adducts, polymeric or oligomeric NO adducts; anti-coagulants such as D-Phe-Pro-Arg chloromethyl ketone, an RGD peptide-containing compound, heparin, antithrombin compounds, platelet receptor antagonists, anti-thrombin antibodies, anti-platelet receptor antibodies, enoxaparin, hirudin, Warafin sodium, Dicumarol, aspirin, prostaglandin inhibitors, platelet inhibitors and tick antiplatelet factors; vascular cell growth promoters such as growth factors, growth factor receptor antagonists, transcriptional activators, and translational promoters; vascular cell growth inhibitors such as growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin; cholesterol-lowering agents; vasodilating agents; agents which interfere with endogeneous vasoactive mechanisms; survival genes which protect against cell death, such as anti-apoptotic Bcl-2 family factors and Akt kinase; and combinations thereof.

Examples of polynucleotide sequences useful in practice of the invention include DNA or RNA sequences having a therapeutic effect after being taken up by a cell. Examples of therapeutic polynucleotides include anti-sense DNA and RNA; DNA coding for an anti-sense RNA; or DNA coding for tRNA or rRNA to replace defective or deficient endogenous molecules. The polynucleotides of the invention can also code for therapeutic proteins or polypeptides. A polypeptide is understood to be any translation product of a polynucleotide regardless of size, and whether glycosylated or not. Therapeutic proteins and polypeptides include as a primary example, those proteins or polypeptides that can compensate for defective or deficient species in an animal, or those that act through toxic effects to limit or remove harmful cells from the body. In addition, the polypeptides or proteins useful in the present

invention include, without limitation, angiogenic factors and other molecules competent to induce angiogenesis, including acidic and basic fibroblast growth factors, vascular endothelial growth factor, hif-1, epidermal growth factor, transforming growth factor  $\alpha$  and  $\beta$ , platelet-derived endothelial growth factor, 5 platelet-derived growth factor, tumor necrosis factor  $\alpha$ , hepatocyte growth factor and insulin like growth factor; growth factors; cell cycle inhibitors including CDK inhibitors; anti-restenosis agents, including p15, p16, p18, p19, p21, p27, p53, p57, Rb, nFkB and E2F decoys, thymidine kinase ("TK") and combinations thereof and other agents useful for interfering with cell proliferation, including agents for treating 10 malignancies; and combinations thereof. Still other useful factors, which can be provided as polypeptides or as DNA encoding these polypeptides, include monocyte chemoattractant protein ("MCP-1"), and the family of bone morphogenic proteins ("BMP's"). The known proteins include BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 (Vgr-1), BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, 15 BMP-14, BMP-15, and BMP-16. Currently preferred BMP's are any of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 and BMP-7. These dimeric proteins can be provided as homodimers, heterodimers, or combinations thereof, alone or together with other molecules. Alternatively or, in addition, molecules capable of inducing an upstream or downstream effect of a BMP can be provided. Such molecules include 20 any of the "hedgehog" proteins, or the DNA's encoding them.

The present invention is also useful in delivering cells as the therapeutic agent. Cells can be of human origin (autologous or allogeneic) or from an animal source (xenogeneic), genetically engineered if desired to deliver proteins of interest at a delivery or transplant site. The delivery media is formulated as needed to maintain 25 cell function and viability.

Those skilled in the art will recognize that the present invention may be manifested in a variety of forms other than the specific embodiments described and contemplated herein. Accordingly, departures in form and detail may be made without departing from the scope and spirit of the present invention as described in 30 the appended claims.

What is claimed is:

1. A catheter for delivering a fluid to an injection site in heart tissue, comprising:  
a shaft having a proximal end, a distal end and an infusion lumen extending therein, the distal end of the shaft including a penetrating member having an injection port, wherein the penetrating member penetrates the heart tissue at the injection site in a first direction, and wherein the injection port directs fluid in a second direction different from the first direction such that fluid leakage from the injection site is reduced.
2. A catheter as in claim 1, wherein a plurality of injection ports are utilized.
3. A catheter as in claim 2, wherein about 2 to about 100 injection ports are utilized.
4. A catheter as in claim 2, wherein each of the plurality of injection ports have a diameter of approximately 1 to 500 microns.
5. A catheter as in claim 1, wherein the second direction is generally lateral to the first direction.
6. A catheter as in claim 1, wherein the second direction is at an angle of about 5 to about 90 degrees relative to the first direction.
7. A catheter as in claim 6, wherein the first direction is generally orthogonal to the heart tissue at the injection site.
8. A catheter as in claim 1, further comprising a sheath disposed about the shaft.
9. A catheter as in claim 8, wherein the sheath has a proximal end, a distal end and a lumen disposed therein.

10. A catheter as in claim 9, wherein the distal end of the sheath includes a suction head.

11. A catheter as in claim 1, wherein the penetrating member has an outer diameter in the range of approximately 10 microns to 1.25 mm.

12. A catheter as in claim 11, wherein the penetrating member has an exposed length in the range of approximately 1 to 10 mm.

13. A catheter system for delivering a fluid to heart tissue, comprising:  
a pressurized fluid source containing a fluid therein; and  
a catheter having a proximal end, a distal end and an infusion lumen extending therein, the proximal end of the catheter connected to the pressurized fluid source, the infusion lumen in fluid communication with the fluid contained in the pressurized fluid source, the distal end of the catheter including an axial penetrating member having a plurality of lateral injection ports, each of the injection ports being in fluid communication with the infusion lumen such that fluid from the pressurized fluid source may be delivered to the heart tissue via the injection ports.

14. A catheter system as in claim 13, wherein the pressurized fluid source is pressurized to a relatively low pressure of less than approximately 1 ATM to reduce tissue trauma.

15. A catheter system as in claim 13, wherein the pressurized fluid source is pressurized to a relatively high pressure of greater than approximately 100 ATM to increase tissue penetration.

16. A catheter system as in claim 13, further comprising:  
a vacuum source; and  
a sheath disposed about the catheter, the sheath having a proximal end, a distal end and a suction lumen disposed therein, the proximal end of the sheath connected to the vacuum source with the suction lumen of the sheath in fluid communication with the vacuum source, wherein the distal end of the sheath is disposed adjacent the heart

tissue such that the distal end of the sheath is stabilized against the heart tissue when a vacuum is applied to the suction lumen using the vacuum source.

17. A method of delivering a fluid to an injection site in heart tissue of a patient, comprising the steps of:

providing a catheter comprising a shaft having a proximal end, a distal end and an infusion lumen extending therein, the distal end of the catheter including a penetrating member and an injection port;

inserting the catheter into the patient;

navigating the catheter until the distal end of the catheter is positioned adjacent the injection site;

actuating the penetrating member such that the penetrating member penetrates the heart tissue at the injection site in a first direction; and

injecting the fluid into the heart tissue via the injection port in a second direction different than the first direction.

18. A method of delivering a fluid as in claim 17, wherein less than approximately 100 microliters of fluid is injected into the heart tissue via the injection port.

19. A method of delivering a fluid as in claim 17, wherein the catheter includes a plurality of injection ports, and wherein fluid is injected into the heart tissue via the injection ports.

20. A method of delivering a fluid as in claim 19, wherein approximately 1 to 20 microliters of fluid is injected into the heart tissue via the injection ports.



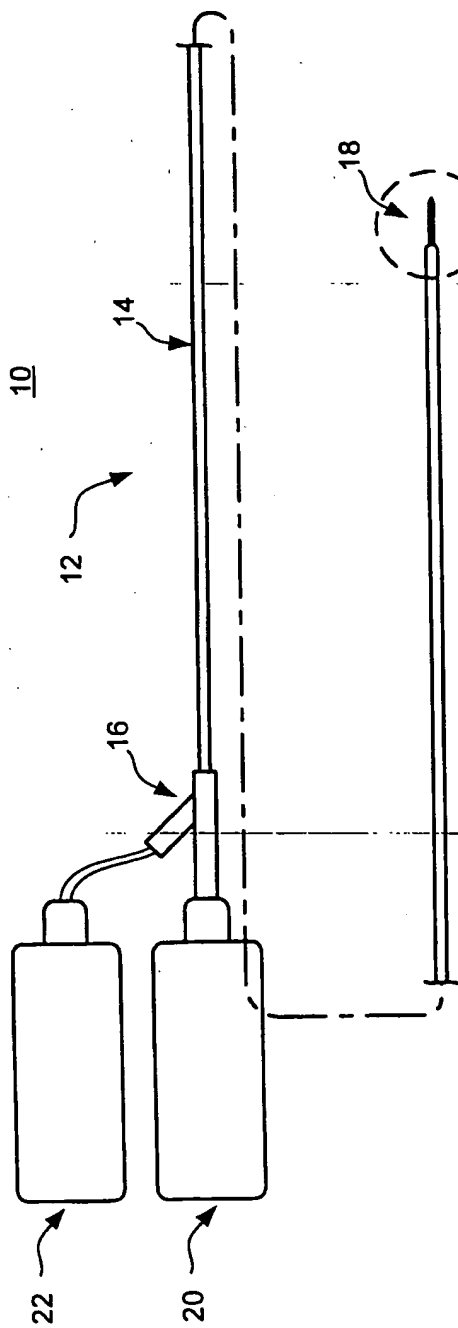


FIG. 1A

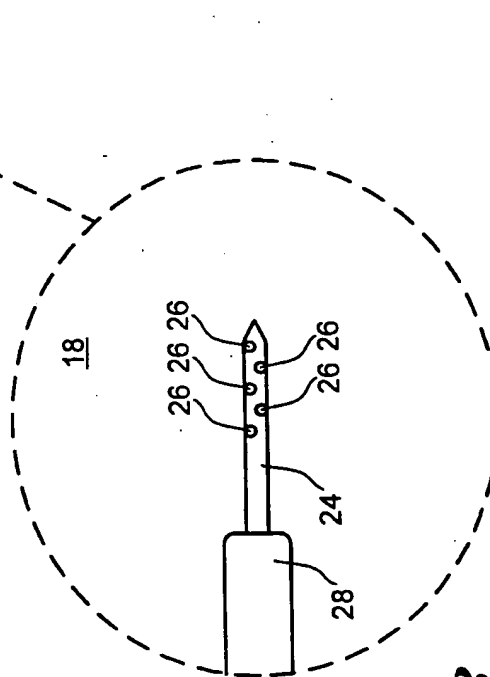
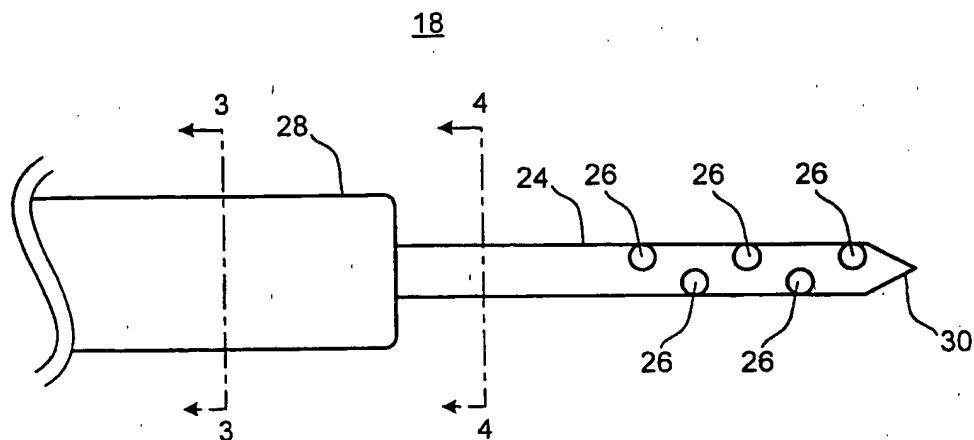
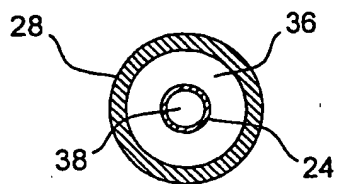


FIG. 1B

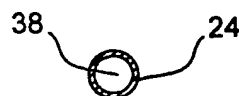
2/4



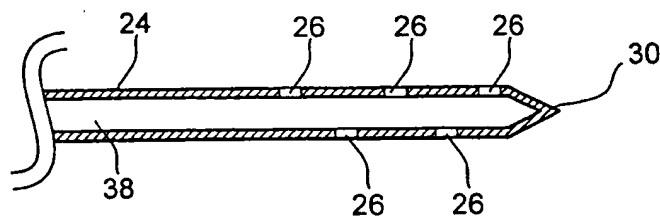
**FIG. 2**



**FIG. 3**

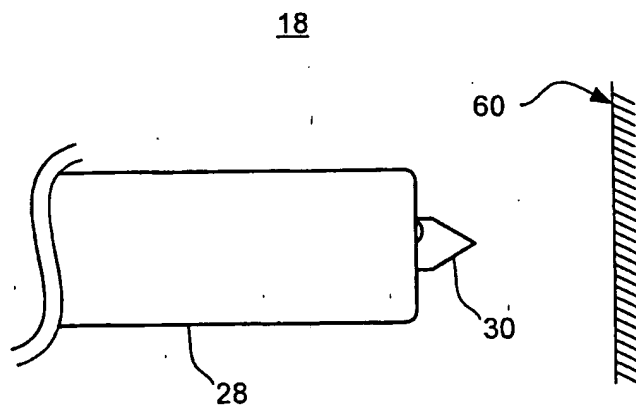
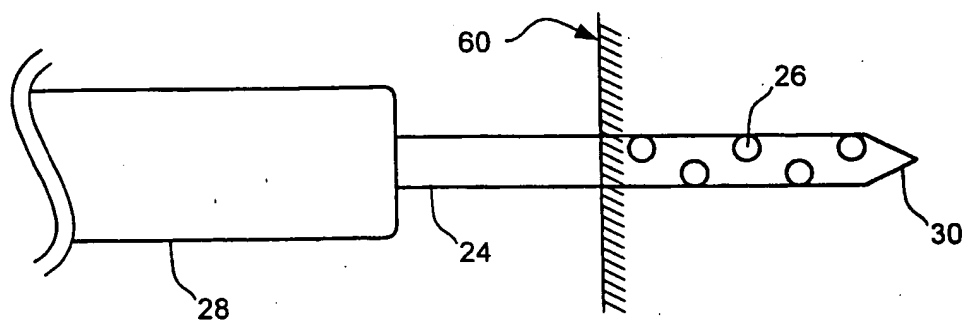
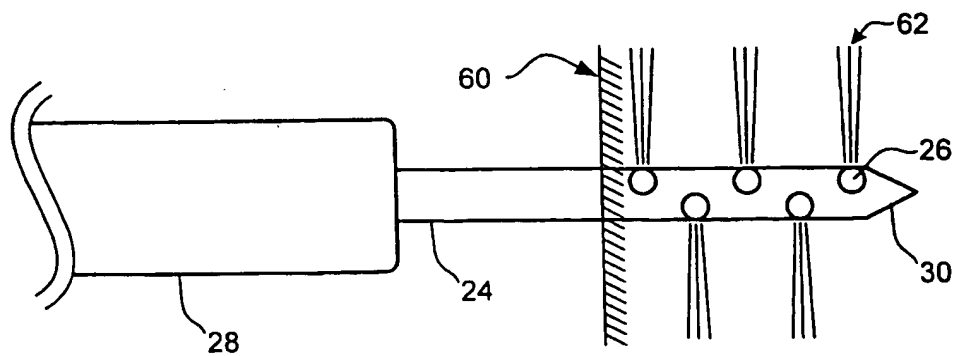


**FIG. 4**



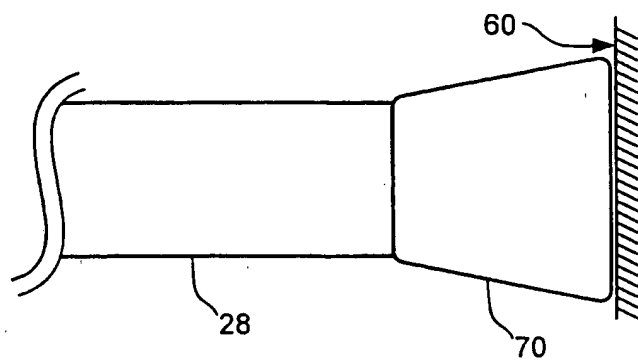
**FIG. 5**

3/4

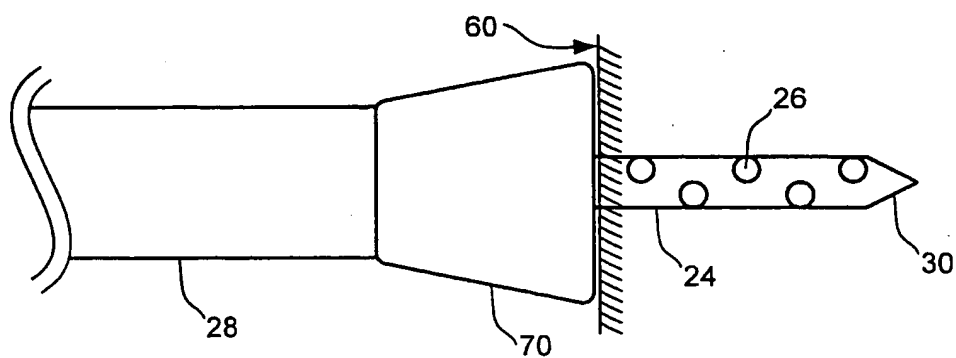
*FIG. 6A**FIG. 6B**FIG. 6C*

4/4

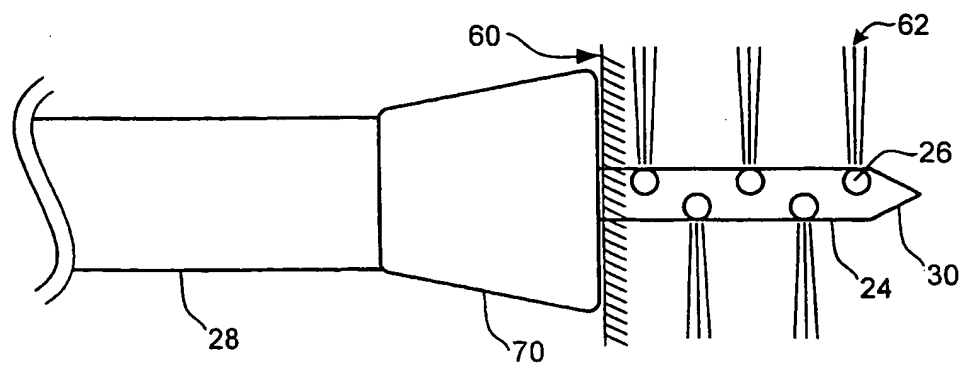
18



*FIG. 7A*

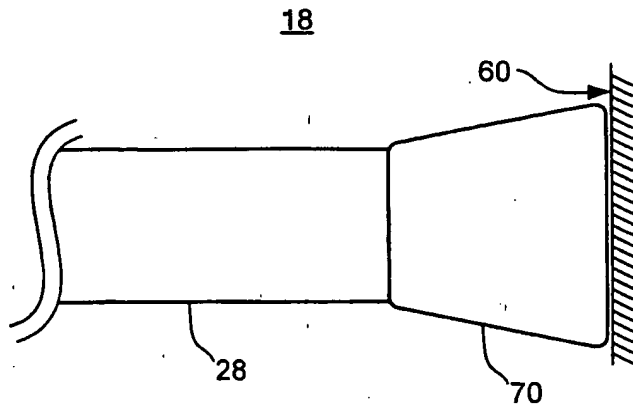
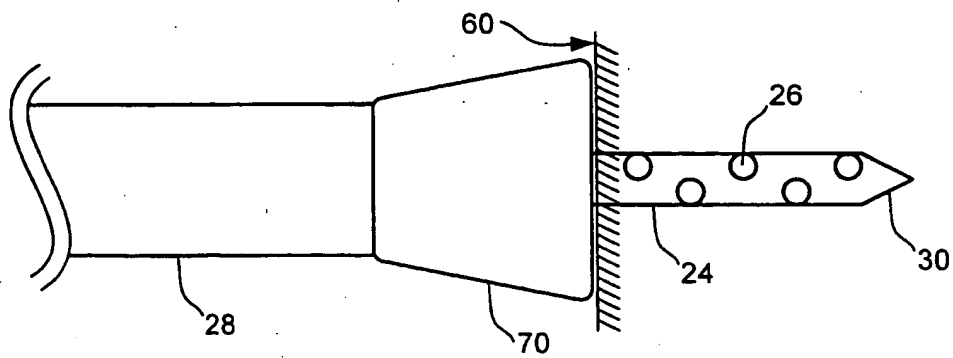
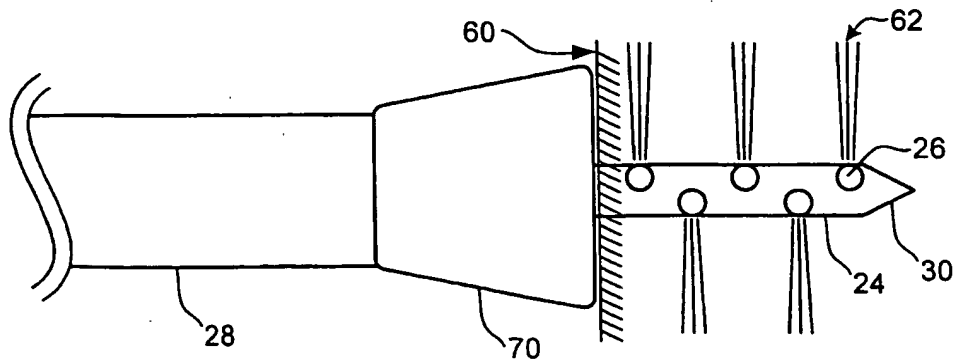


*FIG. 7B*



*FIG. 7C*

4/4

**FIG. 7A****FIG. 7B****FIG. 7C**

## PC 1/US 00/28375

IPC 7 A61B17/22 A61M25/00

According to International Patent Classification (IPC) or to both national classification and IPC

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61B A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages                                   | Relevant to claim No. |
|------------|--|-----------------------|
| X          | WO 99 04851 A (EMED CORP)<br>4 February 1999 (1999-02-04)<br>page 6, line 33 -page 9, line 2; figure 3<br>---        | 1-15                  |
| X          | WO 99 49926 A (CARDIOGENESIS CORP)<br>7 October 1999 (1999-10-07)<br>page 21, line 11 - line 21; figures 5,10<br>--- | 1-15                  |
| X          | EP 0 934 728 A (ECLIPSE SURGICAL TECH)<br>11 August 1999 (1999-08-11)<br>paragraph '0075!; figure 10<br>---          | 1-16                  |
| A          | US 5 840 061 A (KLOPFENSTEIN DENIS ET AL)<br>24 November 1998 (1998-11-24)<br>abstract<br>---<br>-/--                | 1-16                  |

**X**

Further documents are listed in the continuation of box C.

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Patent family members are listed in annex.

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Date of the actual completion of the international search

9 February 2001

Date of mailing of the international search report

15/02/2001

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Clarkson, P

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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| A          | <p>US 5 882 332 A (WIJAY BANDULA)<br/> 16 March 1999 (1999-03-16)<br/> the whole document<br/> -----</p> | 1-16                  |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/28375

| Patent document<br>cited in search report |   | Publication<br>date | Patent family<br>member(s)  | Publication<br>date  |
|---|---|---------------------|---|--|
| WO 9904851                                | A | 04-02-1999          | AU 8659598 A<br>EP 0932428 A  | 16-02-1999<br>04-08-1999   |
| WO 9949926                                | A | 07-10-1999          | AU 3374799 A  | 18-10-1999   |
| EP 0934728                                | A | 11-08-1999          | US 6156029 A<br>JP 11253451 A   | 05-12-2000<br>21-09-1999   |
| US 5840061                                | A | 24-11-1998          | DE 29507987 U<br>AT 176872 T<br>AU 705052 B<br>AU 5897296 A<br>CA 2195219 A<br>DE 59601342 D<br>WO 9636381 A<br>EP 0771219 A<br>ES 2129265 T<br>JP 10513391 T | 19-09-1996<br>15-03-1999<br>13-05-1999<br>29-11-1996<br>21-11-1996<br>01-04-1999<br>21-11-1996<br>07-05-1997<br>01-06-1999<br>22-12-1998 |
| US 5882332                                | A | 16-03-1999          | NONE  |  |